Characterization of DILI Risk from Post-Marketing Reports

January 26, 2006

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DILI Risk Assessment Functions

Post-marketing

- **Detection & evaluation of safety signals**
- **Assessment of epidemiological risk**
- **Analysis of phase IV studies**

Pre & Peri Drug Approval

- **Determination of appropriate risk management measures based on risk/benefit profiles**

Overview of Presentation

- **Tools used by DDRE to detect & characterize DILI risk**
- **Approaches to develop & assess an AERS case series**
  - **characteristics of interest**
  - **causality assessment**
  - **search strategy and case definition steps**
- **Tools limitations in spontaneous report & reporting rate interpretation**
  - **clinical trial to elucidate AERS DILI signal**
  - **safety data bases**
  - **epidemiological databases**
- **Summary**

Post-Marketing DILI Association
Sources of Information

- **AERS**
  - **Manufacturer's reports**
    - **'15 day' reports; serious unlabeled AEs**
    - **direct reports; often from pharmacists or consumers**
- **International sources**
  - **WHO Uppsala Monitoring Center**
  - **Communications with EMEA, Canada, Australia, New Zealand**
- **Published Literature**
- **Clinical study databases; Pre/Post-approval studies**
- **Epidemiologic / Administrative claims-based databases**
- **? DILIN; ? ALFSG**

Adverse Event Reporting System (AERS)

- **Voluntary, 'spontaneous' reporting system**
  - **– Sponsors required to report (21CFR314.80)**
- **• Computerized database**
- **• Origin 1969; > 3 million reports of human drugs & therapeutic biologics (not vaccines)**
- **• Especially useful to detect safety signals with rare background rates, short latencies not confounded by other Rxes or medical conditions**
- **• NMEs can be screened with data-mining to measure disproportionality of AEs using Bayesian approach**

Evaluation of DILI with *AERS*

- ***Search*** **using MedRA terms (PT, HLT, HLGT, SOC) is broad**
  - **MedRA terms used include: Hepatic Failure & Associated Disorders (HLT), Hepatic Fibrosis and Cirrhosis (HLT), Hepatic Necrosis (PT), Hepatitis Fulminant (PT), Liver Transplant (PT)**
- ***Case definition*** **is used to refine series by exclusion of non-pertinent cases obtained in search. Criteria of dx, range of injury type/severity, clinical/lab information can be included**
  - **'Acute Liver Failure': Lab evidence of hepatic necrosis, onset of symptoms/signs temporally related to drug; Encephalopathy; No serological evidence of viral hepatitis; No competing causes of acute liver insult, progressive liver disease or other hepatotoxic drugs**

Evaluation of DILI with *AERS*

- **AERS limitations**
  - **Extensive fluctuation in reporting levels & under-reporting**
  - **Variability in quality of reports**
- **Calculation of AE reporting rates**
  - **Numerator: number of de-duplicated case reports**
  - **Denominator: measure of drug exposure**
  - ***Not a measure of true incidence***
  - **May be compared to background rate(s) in population**
- **Causality analysis**

Evaluation of DILI with *AERS* *Causality Assessment*

- **Causality scoring of *individual* cases performed as a *distinct* analysis of signal strength**

- **Inconsistencies in expert scoring often due to differences in weight given to**
  - **– presumed mechanism(s) of liver injury by suspect drug (e.g. idiosyncratic hepatocellular necrosis, cholestatis, mitochondrial toxicity, autoimmune)**
  - **– confounding factors (other liver disease(s), toxic drug(s), etc.)**
  - **– absence of important diagnostic information**
  - **– assumptions about converging/synergistic liver injury pathways (e.g. Are pathways of injury unrelated? Is severity of injury determined by additive effects of separate processes? Is there a threshold of injury which depends on synergism between 2 pathways?)**

Evaluation of P-M DILI Case Series
Characteristics of Interest (1)

- **Are the numbers of reported cases of clinically significant DILI disproportionate with respect to other AEs?**
- **What is the range/distribution of clinical severity of liver injury among the cases?**
- **What are relationships between suspect drug dose, duration of exposure & patient susceptibility factors with liver injury?**
- **Is there a signal of liver injury in the clinical trial safety database typically based on imbalances between drug & placebo/comparator arms of RCTs? (mild/reversible serum transaminase elevations? Hy's cases?)**
- **What are the patterns of liver injury? Are these distinct from those associated with an underlying disease or concomitant drug?**

Evaluation of P-M DILI Case Series

Characteristics of Interest (2)

- **How many cases are confounded by underlying disease or concomitant drugs that cause liver injury?**
- **What is the range and distribution of causality assignments in cases with clinically significant DILI (highly likely, probable, possible, unlikely, etc.)? How many 'likely' or 'probable' cases are there?**
- **Is the suspect drug an unambiguous cause of liver injury in some cases?**
- **Based on usage, what burden (incidence and range of clinical outcomes) of adverse events might be projected in the US population?**

Causality Assessment
Possible Scenarios

- **Differences in scoring among experts**
  - **small vs wide variations**
- **Number of cases that meet case definition**
  - **small vs large numbers**
- **Distribution of scores**
  - **all cases scored in ‘unlikely’ & ‘possible’ range vs some in ‘probable’ & ‘likely’ range**

Causality Assessment of AERS Cases

Link to population based risk?

- **Case series is not a prospective controlled experiment**
- **P*resence* of 'likely' cases is helpful since it demonstrates that the suspect drug causes DILI**
- **A*bsence* of 'likely' cases does not exclude a causal association with the suspect drug, especially when concomitant factors are necessary for injury to occur. Other drugs/confounding causes of liver injury may be synergistic or additive with DILI induced by the suspect drug**
- **Risk evaluation should take into account other pertinent info**
  - **clinical trial data**
  - **common structures or modes of action in drug class**
  - **plausible mechanism(s) of liver injury**
    - **distinct clinical/laboratory characteristics?**
    - **signature temporal or dose effects?**
    - **typical LFT profile?**

Causality Assessment of Individual Cases
Bayesian Probability Approach

$$\frac{P(D \rightarrow E) \mid B, C}{P(D \not\rightarrow E) \mid B, C} \sim \frac{P(D \rightarrow E) \mid B}{P(D \not\rightarrow E) \mid B} \times \frac{P\ C \mid (D \rightarrow E)}{P\ C \mid (D \not\rightarrow E)}$$

Posterior Odds (Overall Probability)	Prior Odds (Clinical trial & Epidemiologic data)	Likelihood Ratio (Individual case data for causality)

Legend

P:	Probability	B: Baseline information
$D \rightarrow E$:	Drug caused event	C: Case event
$D \not\rightarrow E$:	Drug did not cause event	

*From: Pharmacoepidemiology, Fourth Edition (2005); Determining Causation from Case Reports; Judith K. Jones; Ed. B.L. Strom

Causality Assessment
Bayesian Probability Approach

- **Posterior (overall) probability of individual case causation by a suspect drug based on:**
  - **– what is known about (quantitative) probability of drug causation prior to event**
  - **– causality assessment of individual case**
- **Presence of some 'likely' or 'probable' cases consistent with a significant risk for DILI**
- ***Proportion* of 'likely' cases in the series cannot be translated to a 'prior odds' factor to assess an individual case since the series may not be representative of all cases in the population**

Tools to ‘take measure’ of an AERS DILI signal

- **Spontaneous reports of severe DILI, ALF, liver-related deaths; numbers & reporting rates**
- **Clinical trial database sufficiently powered to enable projection of incidence or other quantitative measures of drug related risk**
- **Epidemiologic database(s) linked to medical records with sufficient drug exposure to enable case control or cohort studies of DILI**

‘Serious’ Hepatotoxicity AERS Reports * US Crude Counts: 5 Drugs

	2001-2002	2003-2004
Acetaminophen	145	223
Troglitazone	222	1
Clavulanate	1	2
Valproic Acid	7	1
Isoniazid	5	9
Phenytoin	14	9

***Duplicate reports included. MedDRA terms: Hepatitis Fulminant (PT), Liver Transplant (PT), Hepatic Necrosis (PT), Hepatic Failure and Associated Disorders (HLT), Hepatic Fibrosis and Cirrhosis (HLT)**

AERS Report Numbers
'Liver' Signal Characterization

- **Even without quantitative risk info, consistently higher numbers of 'serious' liver injury/ALF reports (e.g. APAP and troglitazone) are consistent with higher DILI frequencies**
- **In the absence of reliably measured usage between products reporting rate comparisons are not possible**
- **'Weber' effect pertains to reduced AE report numbers of older products**

Clinical Trial Safety Databases
Risk projection/confirmation

Things to look for:

- **Imbalances of transaminase elevations; drug vs placebo**
- **Hy's cases**
- **Equivalent enrolled patients and study protocols which may enable safety outcome comparison with other agents**
- **Randomized comparisons of safety outcomes between therapeutic agents/members of a class**

Study protocol caveats:

- **Were patients with susceptibility factors enrolled?**
- **Was threshold dose/duration/exposure for toxicity exceeded?**
- **Was LFT monitoring and F/U adequate?**
- **'Capping' risk for rare serious outcomes is linked to study power (drug exposure)**

Thiazolidinediones

NDA Safety Databases & ALF Reporting Rates

		Clinical Trial Data			*AERS*
Drug	***n***	***% ALT>3xULN***	***% ALT>10xULN***		***ALF fatal + x-plant report rate per 10^6 pt-yrs***
Troglitazone	2,510	1.9	0.68		63
Placebo	475	0.6	0		
Rosiglitazone	3,503	0.2			3*
Placebo	574	0.2			
Pioglitazone	1,526	0.3			4*
Placebo	793	0.3			

*1999-2004

Troglitazone
NIH Diabetes Prevention Trial

- **585 patients Rxed with Troglitazone**
- **ALT > 3X ULN: 18/585 (3.0%)**
- **ALT > 8X ULN: 9/585 (1.5%)**
- **ALT > 30X ULN: 2/585 (0.3%)**
- **ALF: 1/585 (rate ~ 1,724 per 10^6 pt-yrs*)**

*** 95% CI: 44 - 9,569 per 10^6 pt-yrs; ALF background rate ~ 1 per 10^6 pt-yrs based on epidemiologic studies in US, Canada & U.K.; FDA Metabolic-Endocrine Drugs AC, March 26, 1999**

Epidemiological Databases

Risk projection/confirmation

- **Large health care organizations; claims data linkage to Rx info; access to medical records**
- **Case control & observational retrospective inception cohort designs**
- **Often sufficient drug exposure to detect rare AEs**
- **Analysis depends on**
  - **– sufficient drug exposure; lag effect after drug is introduced into market; analysis often antecedes initial AE signal detection**
  - **– reliable/consistent disease classification (ICD codes); validation required**
- **Analysis limited if**
  - **– high AE background rates**
  - **– results not generalizable to other populations**
  - **– high patient turnover or loss to f/u**
  - **– incomplete medical records**
  - **– biases in comparator groups**

Troglitazone

*Incidence of ALF/DILI in Health Care Organization**

- **UnitedHealth Group: ~ 3 million persons**
- **Rx 4/97 – 12/98; Completed analysis: 2002**
- **ICD-9 code identified liver cases; Medical records reviewed**
- **7,568 patients Rxed with Troglitazone; 4,020 patient-yrs**
- **19 patients with liver-related hospitalization**
- **5 patients with DILI; Incidence rates (point estimates):**
  - **Hospitalization (n = 5): 1,244/10^6 patient-yrs (95% CI 404 – 2,900)**
  - **Jaundice (n = 4): 995/10^6 patient-yrs (95% CI: 271 – 2,546)**
  - **ALF (n = 1): 240/10^6 patient-yrs (95% CI: 6.3 – 1,385)**
- **Demonstration of range & distribution of clinical outcomes in patients with Troglitazone associated DILI**
- **Results consistent with clinical trial and AERS data; enhance quantitative evaluation of DILI risk although limited by wide CIs**

*** Graham DJ, Drinkard CR & Shatin, D; Am J Gastro, 98 ; 2003**

Summary (1)

- **AERS is a critical surveillance tool to identify drugs that cause DILI & characterize clinical/laboratory features of DILI cases linked to a suspect drug**
- **Causality analysis is useful to determine whether the causal link of a suspect drug with DILI is real, especially if there are 'likely' or 'probable' cases**
- **The presence of a substantial number of 'likely' or 'probable' cases is consistent with increased risk for a suspect drug to induce DILI. Nonetheless, it would be problematic to use the proportion of such cases in a series to inform causality assessments of other cases (using a Bayesian approach) since they are spontaneous reports and are likely not to be representative of all drug-associated cases**

Summary (2)

- **Absence of 'likely' or 'probable' cases does not necessarily correlate with lack of a causal association between a suspect drug and DILI**
- **Confounding factors may be synergistic or additive with a suspect drug to promote hepatotoxicity, sometimes associated with a different clinical/lab signature than with the drug or confounding factors alone**
- **Each methodological approach for DILI risk evaluation has significant limitations**
- **Results of spontaneous reports, clinical trial safety datasets, epidemiological studies & DILI registries complement one another in the detection & characterization of DILI risk**

Backup slides

Clinical Scales of Causality
General Criteria

- Temporal relationship between Rx and liver injury
- Exclusion of alternative Causes
  - caveat: drug-induced toxicity might aggravate injury of underlying chronic liver disease
- Extrahepatic manifestations of hypersensitivity
- Dechallenge/Rechallenge
- Risk factors
- Bibliographic information

- *Although limited because of incomplete info, it is often useful to assign each AERS report of ISLI/ALF/death a 'score' to establish likelihood of causality.*

CIOMS Diagnostic Scale*

Individual Criteria	*Range of Scores*
Time from start of Rx until event	+1 to +2
Time from stop of Rx until event	0 to +1
Course after stop of Rx	-2 to +3
Age	0 to +1
Alcohol/Pregnancy	0 to +1
Concomitant Rx	-3 to 0
Non drug-related causes	-3 to +2
Previous drug information	0 to +2
Dechallenge/Rechallenge	-2 to +3

Causality Assessment: Total Scores

Highly Probable: 8-10; Probable: 6-8; Possible: 3-5; Unlikely: 1-2

*Danan & Benichou, J. Clin. Epidemiol.; 1993

Attribution of Causality to Drug(s) in AERS Reports of Hepatotoxicty

- Rules of differential dx are no different than in pre-marketing studies or at bed-side
- Analysis of causality requires informative reports
  - Accuracy of attribution is enhanced by
    - use of consistent criteria (e.g. CIOMS, CDS or M&V scales)
    - proactively pursuing patient info including medical records
- Absence of adequate info/patient histories is major stumbling block. Lack of critical info does not imply lack of causality!
- Presence of underlying liver disease may cause confusion